REMARKS

A check for the fees for an extension of time for three months of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050.

Claims 50-52, 73-79, 81, 84, 87-95, 97-99, 101, 104, 108, 111, 114, 115, 117 and 119-121 are pending in this application. Claims 51, 92, 94, 95, 97, 115, 117, 119 are amended. Basis for the amendments can be found in the claims in the original parent, as well as in the instant application and intervening parent application. For example, basis for claim 92 can be found in the specification, for example, at page 19, lines 4-8. No new matter is added. Claims 80, 82, 83, 85, 86, 96, 100, 102, 103, 105-107, 112, 113, 116, 118 and 122-127 are cancelled without prejudice or disclaimer. Applicant reserves the right to file a divisional or continuation application to any cancelled subject matter.

An unexecuted DECLARATION of Stephen Fabijanski (herein DECLARATION 7) pursuant to 37 C.F.R. §1.132 accompanies this response. The executed DECLARATION of Dr. Stephen Fabijanski will be provided under separate cover upon receipt.

Applicant also is mailing a Supplemental Information Disclosure Statement filed under separate cover on the same day as the instant amendment and response.

All Responses and DECLARATIONS of record, including the Response and DECLARATION 1 of Fabijinski filed July 16, 2003; the Response and DECLARATION 2 of Fabijanski, filed April 22, 2004; the Response and DECLARATION 3 of Fabijanski filed January 16, 2005; the Response and DECLARATION 4 of Fabijanski filed November 09, 2005; and the Response and DECLARATION 5 of Fabijanksi and DECLARATION 6 of Hadlaczky filed April 30, 2007, responsive to previous Office Actions are incorporated by reference in their entirety herein.

Preliminary Remarks

The Examiner's rejections and responses to Applicant's arguments appear to be premised on the basis that the Examiner does not believe that SATACs can be generated in plants using methods exactly as described in the application. This premise is incorrect. As described in great detail in previous responses, each incorporated by reference herein, the specification fully describes that the method can be used to generate SATACs in other species, including plants. Applicant also has provided DECLARATIONS

(DECLARATIONS 1-6) that evidence use of the methods as described in the application for generation of SATACs in diverse species, including humans and plants, clearly showing the universality of the method, and also methods of introducing SATACs into plant cells to generate transgenic plants as claimed. For example, using methods as described in the application and known to one of skill in the art as of the earliest filing date, the DECLARATIONS demonstrate (1) the process of generating satellite artificial chromosomes (SATACs) is universal and that the methods are the same in diverse species (DECLARATION 6); (2) the generation and characterization of plants SATACs based on identifying characteristics common to all SATACs (DECLARATIONS, 2, 4, and 5); (3) introduction of SATACs into plants cells (tobacco protoplast cells, Arabadopsis cells and rice protoplast; DECLARATION1); and 4) production of transgenic plants by introducing a SATAC into a plant cell (DECLARATION 3).

The Examiner, therefore, seems to question the validity of statements made by the undersigned, and also sworn statement made under penalty of perjury in DECLARATIONS of record. Furthermore, the Examiner seems to disagree with the *veracity* of the statements provided by the Applicant that the methods taught in the application could generate SATACs in any species. The Examiner has provided no scientifically based explanation for this position. We respectfully remind the Examiner that there is a presumption that statements in applications are true, and that DECLARATIONS include a penalty clause. There is guidance on this matter at MPEP 2107, and case law cited below:

> It is incumbent upon examiner to first establish a <u>prima</u> <u>facie</u> case of non-enablement (<u>In re Arbruster</u>, 512 F.2d 676, 185 USPQ 152 (CCPA 1975); <u>In re Marzocchi</u>, 439 F.2d 220, 169 USPQ 367 (CCPA 1971)[a]s a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing the subject matter sought to be patented <u>must</u> be taken as in compliance with the enabling requirement of the first paragraph of § 112 <u>unless</u> there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
> . . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain <u>why</u> it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure (<u>In re Marzocchi & Horton</u>, 58 CCPA 1069, 439 F. 2d 220, 169 USPQ 367, 369-370 (1971)).

See also, e.g., MPEP 2107:

> Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Applicant now also provides DECLARATION 7 of Fabijanksi. As noted in previous responses, Dr. Fabijanski is the President & CEO of Agrisoma, which was a spin-out company owned by Chromos Molecular Systems, a co-assignee of the application. Agrisoma is a licensee of the application at issue. Chromos Molecular Systems exploits and commercializes satellite artificial chromosomes. Agrisoma was formed to commercialize the plant satellite artificial chromosomes. Agrisoma is a fully funded company with deals of its own for sausage chromosomes and SATACs. Clearly, these entities exist and the products are fungible. As described in the DECLARATION 7 of Fabijanski, Agrisoma produces plant satellite artificial chromosomes and other intermediates, such as cells with sausage chromosomes, as described in the above-captioned application as well as the parent applications. Agrisoma did not further develop the technology, but has used it as described in the application. Plant satellite artificial chromosomes and other amplified forms, such as sausage chromosomes, are produced by the methods and based on the technology as described in the above-captioned application and parent applications. To paraphrase Dr. Fabijanski, all one has to do is introduce a DNA fragment into a plant cell **as described in the application** and "poof" sausage chromosomes and SATACs are formed. This happens reliably and reproducibly. As described in DECLARATION 7, the generations of SATACs in plants has been achieved numerous times by Agrisoma, and by various research groups besides Agrisoma exactly as described in the instant application and parent applications.

Accordingly, in view of the above comments and previous responses of record, and arguments below, Applicant requests allowance of the presently pending claims.

I. REJECTION OF CLAIMS 50-52, 73-115, and 117-127 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 50-52, 73-115 and 117-127 are rejected under 35 U.S.C. §112, first paragraph because it is alleged that, while the specification provides guidance for a satellite

chromosome in mammalian cells, the specification does not provide guidance for any plant artificial chromosome, sequences, or methods of making the same, or any plant cells comprising any artificial chromosome. To support this allegation, the Office Action cites numerous (post filing date) references, that are not relevant to satellite artificial chromosomes, that allegedly demonstrate the state of the art of artificial chromosome technology, differences in the DNA between plant and animals and the lack of knowledge of plant centromeric sequences (Willard *et al.* (2000) *Science*, 17:1308-1309; Bryant *et al.* (2001) *Journal of Experimental Biology*, 52:193-202; Avramova (2002) *Plant Physiology*, 129:40-49; Ferl *et al.* in Buchanan *et al.* (2000) *"Biochemistry and Molecular Biology of Plants,"* American Society of Plant Physiologists, Rockville MD, p. 324; and Hall *et al.* (2004) *Current Opinion in Plant Biology*, 7:108-114. The Office Action concludes that given the state of the art and the disclosures of Willard, Bryant *et al*, Avramova, Ferl *et al*, and Hall *et al*, the unpredictability and the lack of guidance by the specification, undue experimentation would be required by one of skill in the art to identify, isolate, and evaluate the components necessary to produce a SATAC in a plant cell, isolate the SATAC, and/or transform a plant with the SATAC. This rejection respectfully is traversed.

In addition, in the Office Action at page 2-7 (under "Response to Arguments") and again at pages 13-21, the Examiner also addresses Applicant's arguments made in the previous Response mailed April 30, 2007. In addressing Applicant's arguments, the Examiner has not separated rejections for enablement and written description under 112, first paragraph. Since the standards and the law differ between such rejections, the Examiner's "Response to Arguments" related to alleged lack of enablement are rebutted in turn below. The Examiner's remaining "Response to Arguments" related to alleged lack of written description are rebutted later herein under the 112, first paragraph Written Description rejection.

Relevant law

The case law has been discussed in previous responses and is incorporated by reference herein.

Analysis

The remarks/arguments and relevant law provided in previous responses, including the last response submitted April 30, 2007, directed to enablement of the claimed subject matter, including an analysis of the Wands Factors, is incorporated by reference herein. The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether

it would require undue experimentation to make and use the claimed invention. As discussed in detail in previous responses and further below, Applicant respectfully submits that the instant application teaches SATACs, including plant SATACs, and methods of producing the SATACs. The application also teaches introduction of a SATAC, including a plant SATAC, into a cell, including plant cells or protoplasts, and the generation of a transgenic plant therefrom. Based on this and consideration of the other Wands factors, it would not require undue experimentation to produce a plant SATAC, a plant cell with a SATAC or to grow the plant cells under conditions to produce transgenic plants that are within the scope of the claims, in view of the knowledge and level of skill in the art and the teachings and disclosure in the specification regarding methods for generating satellite artificial chromosomes for use in different species.

The Office Action now cites post-filing date references, which allegedly demonstrate differences between chromosomes of plants and animals, thereby demonstrating the lack of guidance and unpredictability of the claimed subject matter and the requirement for undue experimentation to practice the claimed subject matter. Specifically, the Office Action cites Ferl *et al.* in Buchanan et al. "Biochemistry and Molecular Biology of Plants" (2000) American Society of Plant Physiologists, Rockville MD, pg. 324; Willard *Science* 290:1308-1309 (2000); Avramova *Plant Physiology*, 129:40-49 (2002); Hall *et al. Current Opinion in Plant Biology*, 7:108-114 (2004); and Bryant *et al. J. Exp. Med.*, 52:193-202 (2001). Some of these references have previously been cited by the Examiner in the Office Action mailed January 17, 2003, and rebutted by Applicant in the response thereto filed July 16, 2003. Nevertheless, Applicant addresses the present rejection in whole.

It respectfully is submitted that the references cited by the Examiner have no bearing on the reproducibility nor universal applicability of the methods as instantly claimed, namely a method of producing a transgenic plant by introducing a SATAC into a plant cell. None of the references cited by the Examiner offers any evidence that the methods of the instant application do not result in production of plant satellite artificial chromosomes. The DECLARATIONS rebut this assertion; showing that one only has to introduce a fragment of DNA under selective conditions and identify cells that have generated SATACs and/or intermediates or precursors thereof or other amplified chromosomal structures. The skilled artisan does not require knowledge of plant chromosomal structure or sequences or centromeres or other methods. As Dr. Fabijanski has said, one follows the teachings in the specification, and SATACs and sausage chromosomes are produced by the cells.

There is no teaching within the references that would suggest that the methods of the instant application do not work in plants. The absence of the Applicant's claimed subject matter in the literature does not *a priori* support an enablement rejection; it demonstrates its novelty. Such rejections may only be made where individuals of skill in the art state that a particular invention is not possible. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). Since none of the references make such assertions regarding generation of SATACs in plants and the resulting SATACs, use of these post-filing references to evidence non-enablement is improper and inapt. Furthermore, none partake of benefit of the teachings of the instant application, which is a significant factor to be considered in assessing enablement.

Furthermore, DECLARATIONS 5 and 6 provided with the previous response, and the other DECLARATIONS of record, unequivocally establish otherwise. The DECLARATIONS demonstrate that, by following the teachings of the specification, the methods operate as claimed for the generation of plant SATACs. The DECLARATIONS show that the instant application teaches method that are universally applicable to the generation of SATACs in eukaryotes, including the generation of plant SATACs. Further, DECLARATION 7 provided herewith demonstrates the reproducibility of the method, since several research groups, by following the teachings of the specification, have generated SATACs from plants.

As noted, each of the cited references is inapt to the claimed subject matter. Willard is alleged to provide the general state of the art with respect to components of artificial chromosomes and their assembly. Willard does not consider the instant application and its teachings; thus, it does not provide the general state of the art with respect to satellite artificial chromosomes. It respectfully is submitted that Willard provides no teachings relevant to satellite artificial chromosomes nor to the production of satellite artificial chromosomes. Willard makes no mention of satellite artificial chromosomes.

Ferl *et al.* is alleged to describe that the satellite DNA content in plants is different than in animals. While the disclosure of Ferl *et al.* does demonstrate that the sequences of the centromere among species varies, for example, due to the GC-rich satellite DNA in plants versus the AT-rich satellite DNA in animals and yeast, Ferl *et al.* does not provide any teachings that this species variation impacts on the ability to produce satellite artificial chromosomes from any species, nor their introduction into cells. There is nothing on the record that would suggest that the particular satellite DNA content impacts on the formation

of satellite artificial chromosomes. The data in the specification and in the DECLARATIONS demonstrates otherwise. Also, the species variation of centromere sequences, if any, has no bearing on the predictability of the plant SATACs as instantly claimed; there is no need to have any sequence information for preparation of SATACs. Inclusions of targeting sequences is optional; it just increases the occurrence of the incorporation of the introduced DNA fragment into the pericentric heterochromatic region of the chromosome. Nothing need be known about the sequence of the centromere.

Hall *et al.* is alleged to show that many plant centromeric sequences were not known at the time of filing the instant application, and therefore centromeric sequences of the claimed subject matter could not have been known at the time the application was filed. Although Hall *et al.* does disclose that sequencing of the rice and maize centromeres, in particular, were not complete as of its publication, it is respectfully submitted that this point is not relevant to the claimed subject matter. The methods for making satellite artificial chromosomes require no knowledge of centromeric sequences. As described in the last response, DECLARATION 5 of Fabijanski of record and further in DECLARATION 7 provided herewith, no knowledge of plant centromere sequences is required to generate plant SATACs as claimed, and as described in the specification. Further review of the specification renders it clear that knowledge of centromeric sequences is not required.

Bryant *et al.* is cited to support the allegation that the DNA component necessary for an origin of replication in plants was unknown at the time of filing the instant application. Without arguing the propriety of this assertion with respect to the disclosure of Bryant *et al.*, it is respectfully submitted that no knowledge of the origin of replication of plants is required to generate a plant SATAC using the methods as taught in the application. Hence, any species variation in the origin of replication has no bearing on the predictability of the plant SATACs as instantly claimed.

Avramova *et al.* is cited to evidence that the chromosome structure of animals is different than that of plants because allegedly Avramova *et al.* discloses that the patterns of heterochromatin in chromosomes of plants and animals are different, and there are no similar proteins associated with the chromosomes between animals and plants. It is respectfully submitted that Avramova does disclose the location of heterochromatin in plants to the centromeric and pericentromeric regions. For example, the passage at page 40, left column begins "In plants, in addition to the centromeric and pericentromeric regions, heterochromatin is located at the nucleolar organizer..." Accordingly, contrary to the

assertions by the Examiner, this statement by Avramova indicates that heterochromatin is present in corresponding regions in plants and animals, specifically, the centromeric and pericentromeric regions.

The instant methods exploit processes common to plants and animals cells. The DECLARATIONS of record clearly demonstrate this. Any difference between plant and animal heterochromatin, does not impact on practice of the instant claimed methods nor on production of satellite artificial chromosomes. Thus, reliance upon references such as Willard and references that describe other artificial chromosomes is inapt, since the technology therein is unrelated to the technology upon which the instant methods are based, and does not represent the state of the art of satellite artificial chromosome technology. Furthermore, Willard and the other references did not appreciate or take advantage of the instant disclosure, which teaches how to make and use satellite artificial chromosomes. It is the instant Applicant who first invented the satellite artificial chromosomes, and they can be produced by a method, whose steps are outlined in detail in the specification, in any eukaryotic cell that contains chromosomes with amplifiable DNA as taught in the specification

As discussed in detail in previous responses, the teachings in the specification are generally applicable to plants and animals. The specification teaches methods for making SATACs, methods for identifying SATACs, including the elements of SATACs, and exemplary structures, and methods of introducing SATACs into cells. There is nothing in the methods that is peculiar to animal cells. DECLARATION 7 demonstrates that the methods are highly reproducible, since a number of different SATACs were generated in at least two different plant species using the methods as described in the application, and were generated by several research groups. In addition, Agrisoma, the licensee of the instant application, practices the methods in the instant application to produces cells that contain SATACs and other structures for production of transgenics, gene therapy and gene products. As described in the DECLARATION 7 of Fabijanski, the technology used to generate plant SATACs is the same as described in the instant application. The fact that this technology is at the forefront of Agrisoma's business evidences the predictability and universality of SATACs and the method of making SATACs. The basic methods employed are fundamentally the same as in the original application. As discussed in great detail in previous responses, the specification teaches in great detail how to make them, and DECLARATIONS of record, including DECLARATION 5 and 7, evidence that one of skill in the art can make SATACs by

following the teachings of the specification; DECLARATION 6 evidences its universality and reproducibility. Therefore, unpredictability is not a factor weighing against enablement.

Rebuttal to Examiner's Comments

A. Knowledge of the plant centromere sequence is not required to produce or to use a SATAC in the methods as claimed

The Examiner urges that the Applicant's statement that centromeric DNA sequence information is not required for the generation of a satellite artificial chromosome in any eukaryotic cell, including plants, is not persuasive. The Examiner urges that this is because the structure and function of centromeres directly relates to whether or not the artificial chromosomes generated by the claimed methods are enabled, and that the difference between plant centromeres and mammalian centromeres determines whether a chromosome would be formed, and whether or not it would be capable of maintaining the chromosome after cell division. The Examiner further notes that regardless of whether or not centromere sequences are part of the exogenous DNA targeted to the plant chromosomes, the predictability and knowledge of plant centromere function and structure is required to predict whether or not the function and structure are sufficiently similar to mammalian centromeres that the claimed methods would actually occur in plants.

Applicant respectfully disagrees with the Examiner. Applicant steadfastly maintains knowledge of the centromere is not required as the centromere is not the target of the method. No sequence information about any centromere-related chromosomal elements is required. This is true for the generation of SATACs in mammalian species, as well as in any eukaryotic species, including plants. To generate SATACs in any species, including plants, requires simply introducing heterologous DNA into cells, growth of cells and selection of cells containing amplified sequences. Thus, contrary to the Examiner's assertions, there are no centromere sequences that are part of the exogenous DNA targeted to the plant chromosomes. In the method, the nucleic acid randomly integrates into the pericentric DNA or is targeted to the pericentric DNA using a targeting nucleic acid sequence, as exemplified by the use of rDNA, causing a "propagation" of amplification and consequent duplication of the adjacent **endogenous** centromere of the cell. The centromere of the resulting SATAC is generated from the amplification event inside the cell that produces a dicentric chromosome, and ultimately a SATAC. Hence, knowledge of the structure or function of the centromere will not in any way contribute to the success of the method. Even knowing the entire nucleotide

by nucleotide DNA sequence of the centromere would not contribute to the production of SATACs as currently claimed.

The resulting SATACs, generated in any species, **contain** centromeres derived from the eukaryotic cell in which the amplification event took place. As taught in the specification (see e.g., at page 16, line 22 to page 17, line 4; page 34, line 23), the SATAC is stable and can replicate and segregate alongside the endogenous chromosome. The DECLARATIONS demonstrate that plant SATACs are stably maintained in cells, just as taught in the specification. For example, DECLARATION 5 of Fabijanski, shows that selection of tobacco protoplast cultures was carried out 14 to 21 days after heterologous DNA was introduced to protoplasts. After several weeks in culture, analysis of plant cells showed the presence of a SATAC evidencing maintenance of the SATAC during mitosis. Similar SATAC maintenance data is shown for *Brassica napus*,. DECLARATION 7 demonstrates transmission of SATACs, or intermediates and precursors of SATACs, in the analyzed root tips of second generation (regenerated) *Brassica napus* plants. The data were observed after typical plant growth without the need for selection, proving, beyond any doubt, that the SATAC is as stable as a native chromosome. The data show the genetic behavior of the SATACs present in the regenerated plants, and show that regenerated seedlings displayed homozygous, hemizygous or null phenotypes at a predicted Mendelian frequency. Thus, these results show that the generated artificial chromosomes exhibit genetic behavior that is functionally similar to resident chromosomes.

DECLARATION 2 provides additional evidence of the stability of the generated SATACs in *Nicotiana*, where a callus cell line containing a plant artificial chromosome was stably maintained in culture for over six months. DECLARATION 3 also describes the production of transgenic plants containing a SATAC by regeneration of shoots from the calli, and the regenerated plants containing a satellite artificial chromosome flower and set seed. DECLARATION 3 also evidenced the generation of a hybrid transgenic plant by introduction of a plant SATAC by cell fusion, and the regeneration of 50 hybrid plants expressing the marker genes expressed from the SATAC. The regeneration of the plants and the expression of the marker gene evidences the stability of the SATAC in the plant cells; evidences a functional centromere accounting for the maintenance and genetic behavior of the SATAC, including transmissions through thousands of cell divisions and regeneration into a whole plant.

Applicant respectfully submits that there is no better test of chromosome stability than its presence in generation after generation. Furthermore, it is stressed that these SATACs were produced using ONLY a heterologous DNA and a selectable marker without the knowledge of centromere sequences. Using the methods as described in the application, Applicant and others have reproducibly generated SATACs in plants. Thus, Applicant can not reason why the Examiner insists that centromere sequence information is a required element to generate and/or identify a SATAC, given the fact that the Applicant and other research groups have shown the generation and identification of SATACs in numerous species using the exact method as described in the application.

B. DECLARATION 5 of Fabijanski demonstrates the generation of plant SATACs using the methods described in the instant application

The Examiner urges that the DECLARATION 5 of Fabijanski discloses methods not described in the specification, including cytological and transformation techniques. Further, the Examiner states that the cytological techniques appear absolutely crucial to the claimed subject matter, as identification of the artificial chromosomes is crucial to isolation of said chromosomes. The Examiner seems to question the factual data in the DECLARATION 5 of Fabijanski that SATACs are stably generated in plants. The Examiner concludes that the DECLARATIONS may only overcome the enablement rejection if the DECLARATIONS clearly show that the exact method steps taught in the specification were used exactly the same on plant cells and a successful generation, transmission and isolation of a plant SATAC was achieved. The Examiner, however, alleges that in the DECLARATION of record the conditions were modified, and the exact same methods were not used to generate and obtain plant SATACs.

Applicant respectfully disagrees with the Examiners assertions, and submits that the DECLARATION 5 of Fabijanski does teach the generation of a plant SATAC using methods exactly as set forth in the specification, coupled with what was known to one skilled in the art as of the earliest priority date. DECLARATION 5 of Fabijanski describes the generation of SATACs in plants, in particular *Nicotiana* and *Brassica napus,* using the methods as set forth in the application. For example, under the heading "Hosts," at page 51, line 27 to page 52, line 10, the specification teaches that heterologous DNA can be introduced into any host, including animals or plants, using the methods set forth in the application to "produce species-specific artificial chromosomes." *Nicotiana* and *Brassica napus* are exemplified in the subsequent sub-section beginning at page 54, line 1, entitled "Introduction of

heterologous DNA inot plants" as plant species into which heterologous DNA can be introduced for the production of SATACs.

As discussed in detail in previous responses, the methods of generating a SATAC in any species, as taught in the specification, involves the introduction of a heterologous DNA fragment containing a selectable marker that can be inserted randomly into the pericentric region of the endogenous chromosome, or can be targeted to rDNA sequences (see e.g., at pages 29, lines 3-20). The DECLARATION 5 describes the generation of plant SATACs in the two diverse plant species using DNA fragments containing an rDNA targeting sequence and a selectable marker just as taught in the application. Such sequences in plants were known to those of skill in the art at the time of filing the application as described in the previous response and in DECLARATION 5. For example, DECLARATION 5 of Fabijanski describes that the 26S rDNA sequences and the selectable marker sequence used in the method to generate a plant SATAC in both species of plant were known to those of skill in the art at the time of filing the application.. Just as taught in the specification, DECLARATION 5 describes the introduction of the DNA fragments into both plant species using a PEG mediated transfection procedure as taught in the application (see e.g., at page 54, lines 3-7.) The DECLARATION further describes growth of the cells and selection in the presence of a selective agent (L- phosphinothricin (L-PPT)).

Applicant wishes to correct the Examiner's assertion that cytological techniques are crucial to the claimed subject matter because identification is crucial to isolation of SATACs. Such techniques are not necessary for isolation of SATACs, and were not used in the DECLARATION to isolate SATACs. Rather, such techniques are useful for visual characterization of the SATACs. The specification does teach in detail methods of isolating SATACs (see e.g., at page 41, line 4 to page 42, line 3).

Notwithstanding this, Applicant submits that the cytological techniques and the *in situ* hybridization performed on plant cells as set forth in DECLARATIONS of record, including DECLARATION 5, are as set forth in the specification and were well known at the time of filing the instant application. For example, the specification exemplifies formation of a megachromosome, which is a type of satellite artificial chromosome, from a sausage chromosome and teaches the structural features of the megachromosome observed with immunofluorescence, electron microscopy, in situ hybridization, including fluorescence in suit hybridization (FISH) and Southern Blot (see e.g.,, Example 4-7, which describes application of such techniques to identify SATACs, and intermediates of SATACs). As

described in DECLARATION 7 of Fabijanksi, similar cytological techniques, in particular *in situ* hybridization, were standard in plants and known at the time of filing the earliest priority application (see e.g., Leitch *et al.* (1991) *Genome*, 34:329-333; Fukui *et al.* (1994) *Theor. Appl. Genet.*, 87:893-899; Jiang *et al.* (1995) *Proc. Natl. Acad. Sci.* USA, 92: 4487-4491; Murata and Motoyoshi (1995) *Chromosoma*, 104:39-43; Matsuyama *et al.* (1996) *Genome*, 39:941-945; Zhong *et al.* (1996) *Chr. Res.*, 4:24-28; and Schubert I and Wobus U (1985) *Chromosoma*, 92: 143-148).

Thus, it is unclear to why the Examiner asserts that the DECLARATION 5 of record does not use the method exactly as taught in the specification to generate a plant SATAC. As discussed above, the DECLARATION sets forth that the methods can be used to generate SATACs in plants, including in tobacco and monocot and dicot plants, such as *Brassica*. Also, just as is described in the specification, DECLARATION 5 exemplifies introduction of a DNA fragment encoding a selectable marker into plant, and also discloses introduction of a targeting sequence containing rDNA. DNA fragments were introduced into plant cells using polyethylene glycol (PEG)-mediated DNA uptake exactly as taught in the specification. A selective agent was used to select for those cells that had undergone an amplification event, and Southern hybridization and *in situ* hybridization techniques were applied as exemplified in the specification. All of the above are standard methodologies taught in the specification and known in the art. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991).

Furthermore, the Examiner also discounts that DECLARATION 5 even demonstrates the generation of plant SATACs because of alleged unexplained background staining and presence of constrictions. It respectfully is submitted that under the USPTO "Guidelines for Examination of Applications for Compliance with the Utility Requirement", the Examiner must accept as true any credible statement made by an applicant or declarant and may only challenge the statement upon a showing that those of skill in the art would consider the assertion **to have no reasonable scientific basis.**

Applicant respectfully submits that the Examiner has no reasonable scientific basis to doubt the factual assertions of Fabijanski, an expert in plant biology with over 20 years of experience in the area of plant molecular biology, plant gene expression, plant tissue and cell culture and development of techniques to produce genetically modified plants and plant artificial chromosomes. The DECLARATION 5 of Fabijanski demonstrates the generation of a SATAC in *Nicotiana*, as evidenced by Figure 3, and in *Brassica Napus*, as evidenced in

Figure 4. Among the intermediates and precursors generated, the SATACs were identified by the characteristics described in the application, i.e. by the presence of a substantial amount of amplified pericentric heterochromatic DNA and a selectable marker on a separate, stable chromosome structure. Further, in DECLARATION 7, Fabijanski states that the images set forth in the DECLARATION are what is commonly seen in the laboratory, and describe what those who routinely analyze thousands of these chromosome spreads have determined to be a dicentric chromosome, sausage chromosome or SATAC.

The Examiner also states that the DECLARATION provides no demonstration that the claimed SATACs are maintained in dividing cells, and thus that there is no evidence of a functional centromere in the resulting SATACs. Applicant respectfully disagrees for the reasons set forth above in rebuttal A) above. DECLARATIONS of record, including DECLARATION 5 and DECLARATION 7 provided herewith exemplify the stable maintenance and transmission of SATACs, including their maintenance through mitosis and meiosis.

C. DECLARATION 2 of Hadlaczky factually evidences the universality of generating SATACs in any eukaryotic cells, including animal and plants

The Examiner urges that the DECLARATION 6 of Hadlaczky is not persuasive because it evidences generation of mammalian SATACs which is not relevant to the instant claims. The Examiner also alleges that the DECLARATION 6 of Hadlaczky provides only an opinion as to the generation of plant SATACs instead of any evidence. Applicant respectfully disagrees.

The DECLARATION 6 was provided to evidence the universality of the underlying chromosomal processes involved in the generation of SATACs and of the process for production of SATACs described in the application and the SATACs described in the application. In the DECLARATION, Dr. Hadlaczky states that the method is based upon fundamental process of chromosomal replication common to plants and animals. This is a statement of fact (the fact that the processes are common to plants and animals), not opinion. To evidence that these processes occur, the DECLARATION 6 of Hadlaczky describes the generation of satellite artificial chromosomes from human chromosomes through the introduction of foreign DNA including a selectable marker into human/hamster hybrid cells containing human chromosomes. The DECLARATION 6 also *incorporates by reference* DECLARATION 5 of Fabijanski, showing the generation of SATACs in plants. The DECLARATION 6, thus, demonstrates that by following the teachings of the application,

SATACs from diverse species, plants and mammals, have been prepared by the methods taught in the specification evidencing the **fact** of the universality of the underlying processes.

D. The specification teaches, and the DECLARATIONS further evidence, the introduction of SATACs into plant cells commensurate in scope to the claimed subject matter

The Examiner alleges that the specification only teaches methods of transformation options of DNA constructs into cells but does not teach introduction of SATACs into plant cells. Applicant respectfully disagrees.

The specification describes methods of introducing artificial chromosomes, such as SATACs, into plant cells. For example, the specification teaches numerous methods for introducing SATACs into a cell (see *e.g*,. page 10, lines 30 to page 11, line 4). Such methods include direct DNA transfer, electroporation, lipid-mediated transfer, e.g., lipofection and liposomes, microprojective bombardment, and microinjection (see, for example, pages 48-56). The specification teaches that chromosomes can be transferred by preparing microcells containing a satellite artificial chromosome and then fusing with selected target cells. Cell fusion can be used to transfer SATACs. Cell fusion also is exemplified in Example 1. DECLARATION 1 exemplifies microcell fusion and lipid-mediated transfer for introducing SATACs into plant cells.

The Examiner's comment that there are only working examples for mammalian cell lines and no other species is not dispositive. Because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). A patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). Thus, there is no requirement for disclosure of every species within a genus.

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it

would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. Here, the specification teaches methods of introducing heterologous DNA and SATACs into cells, and the DECLARATIONS exemplify that the methods work as taught in the specification in diverse species, including plants and animals. Thus, Applicant respectfully submits that one of skill in the art can readily identify, make and use SATACs, inclucing plant SATACs and introduce SATACs into plant cells to generate transgenic plants without undue experimentation.

E. The method as claimed for the generation of plant SATACs, and the resulting plant SATACs and transgenic plants are not unpredictable

The Examiner alleges that there are many differences between plant and animal cells that would make it unpredictable to apply the method as claimed to plants. For example, the Examiner states that routine experimentation would not overcome the obstacles that the plant cell wall poses, nor the vastly different DNA compositions of plant, nor the differences in misdivision between plant and animal cells when it comes to chromosomes segregation. According to the Examiner, the cytological technique differences alone prevent one from merely applying the methods taught in the specification to plant cells. The Examiner further urges that the state of the art as evidenced by the references cited in the previous Office Action evidence the unpredictability of applying such teachings from mammalian systems to plant systems. Also, the Examiner states the unpredictability has not been overcome because the transmission of SATACs has not been demonstrated and the introduction of SATACs into plants has not been demonstrated.

Applicant respectfully disagrees. First, it is unclear to which references cited in the previous Office Action the Examiner is referring to evidence unpredictability of the claimed methods. Notwithstanding this, Applicant submits that the Applicant in the instant application, and priority applications, was the first to disclose SATACs and the generation of SATACs in any eukaryotic species. It is respectfully submitted that references that lack teachings directed to plant SATACs, provide no evidence as to the predictability of SATAC generation and maintenance in cells.

The claimed methods are directed to the *de novo* formation of chromosomes, including SATACs. As previously discussed (in detail), no knowledge of any chromosomal sequence, including the knowledge of the centromere sequence, is required to generate SATACs, including SATACs in plants. Therefore, because no reference that Applicant is

aware is directed to generation of SATACs in plants and the resulting SATACs, use of references, such as post-filing date references cited in the instant Office Action (discussed above), to evidence non-enablement is improper. Furthermore, none partake of benefit of the teachings of the instant application, which is a significant factor to be considered in accessing enablement. Therefore, it respectfully is submitted that the cited references do not weigh on the predictability of the claimed method for generating SATACs in plants and the resulting plant SATACs and use of such SATACs to generate transgenic plants.

Notwithstanding the above, the DECLARATIONS of record, and provided herewith, evidence the generation of SATACs in plants. Thus, these DECLARATIONS unequivocally establish the predictability of the method as claimed of generating SATACs in plants. The DECLARATIONS demonstrate that by following the teachings of the specification, the methods operate as claimed for the generation of plant SATACs. The DECLARATIONS show that the instant application teaches methods that are universally applicable to the generation of SATACs in eukaryotes, including the generation of plant SATACs. As discussed above, the DECLARATIONS also provide evidence of the transmission and stability of SATACs in plant cells. Also, as discussed above, the DECLARATIONS evidence the introduction of SATACs into plant cells. Therefore, the DECLARATIONS of record establish that the claimed subject matter is predictable based on the methods and description set forth in the specification. The Examiner must give deference to the teachings of the specification and to the DECLARATIONS, unless it is shown that one of skill in the art would have a rational basis to doubt the truth of such statements

Agrisoma Biosciences, the licensee of the instant application, was founded on the exploitation of generating plant SATACs as described in the instant application. The methods employed by Agrisoma Biosciences to generate plant SATACs are fundamentally the same as described in the specification. Given that the generation and use of plant SATACs is the cornerstone of a company, further points to the predictability of the method, and resulting SATACs, as claimed.

It respectfully is submitted that the Examiner is required to do more than just categorically make statements such as (see Office Action, Page 17 and 18):

> Routine experimentation would not overcome the obstacles the plant cell wall poses, nor the vastly different DNA compositions of plants, nor the differences in misdivision between plant and animal cells when it comes to chromosome segregation. The cytological technique differences alone

> prevent one from merely applying the methods taught in the specification to plant cells.

Judicial notice cannot be taken unless the facts are capable of "instant and unquestionable demonstration."

The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

In this instance, it is not "unquestionably demonstrable" that the methods as taught in the specification do not work in plants. To the contrary, Applicant has providing DECLARATIONS evidencing the universality of the method, and the generation of SATACs in plants. DECLARATION 6 of Hadlaczky demonstrates that the process as described in the application is fundamental to chromosome replication and universally shared among plants and animals. DECLARATIONS of Fabijanski, including DECLARATIONS 5 and 7, evidence generation of plant SATACs by those who routinely analyze such structures, and demonstrate that such SATACs have been generated numerous times exactly as described in the specification and by numerous research groups. The Examiner is required to provide documentary evidence to substantiate statements of what was "well-known" with respect to generation of SATACs.

Conclusion and summary

Therefore, based upon arguments made herein and in previous responses, and Applicant's rebuttal to the Examiner's specific points, Applicant submits that it would not require undue experimentation to prepare SATACs from any species, including plants, and to use such SATACs to introduce into plants cells for the generation of a transgenic plant. The generation of SATACs is thoroughly described and taught in the subject specification. The specification describes in extensive detail the preparation, characterization and isolation of satellite artificial chromosomes and provides numerous examples of particular embodiments thereof. The specification also describes that the methods can be used in other species to generate "species-specific" chromosomes, such as plant SATACs. DECLARATIONS of record and provided herewith demonstrate the practice of the methods described in the application results in preparation of SATACs from any species, including mouse, human and diverse plant species, and evidence the generation a transgenic plant by introducing a SATAC into a plant cell as claimed. Hence, the DECLARATIONS also evidence the predictability of

the methods. The level of skill and knowledge of those of skill in the art is high, and the prior art describes all methods needed to practice the methods as claimed in accord with the teachings of the specification.

DECLARATION 7

Notwithstanding the above arguments, to further evidence the generation and stability of plant SATACs using methods as taught in the instant application, attached is a DECLARATION 7 under 37 C.F.R. §1.132 of Steven F. Fabijanski. The DECLARATION 7 incorporates by reference DECLARATION 5 of Fabijanski provided with the last response mailed April 30, 2007.

Dr. Fabijanski is not an inventor of this application, he is a Ph.D. Since those of skill in the art typically have advanced degrees, Dr. Fabijanski, who has a Ph.D. degree, is representative of a person of skill in this art with respect to performing experiments in accord with a disclosed protocol. It is noted that he is an employee of Agrisoma, a company in which Chromos, a former joint owner of this application, has an ownership interest, and which is a licensee of the instant application. In performing or directing the experiments in DECLARATION 7, Dr. Fabijanski followed the teachings in the application.

The DECLARATION 7 incorporates by reference DECLARATION 5, which detailed construction of plant SATACs in two distinct plant species, *Nicotiana* and *Brassica*. DECLARATION 5 showed that by following the teachings of the application as of its earliest filing date, plant SATACs can be generated and maintained in plant cells. The DECLARATION 7 demonstrates that there is nothing special or different about the generation of SATACs in plants beyond what was described in the application and routine in the art at the time of filing the application. Plant SATACs can be generated with no additional experimentation or guidance required. DECLARATION 7 further demonstrates that numerous such SATACs have been generated in *Nicotiana* and *Brassica* and by numerous research groups.

As set forth in the DECLARATION 7, no knowledge of the plant centromere sequence is required. As taught in the above-captioned application, the plant SATACs described in DECLARATION 5 were generated following amplification and the generation of a *de novo* centromere. By virtue of the method, the resulting SATACs contained a functional centromere as evidenced by the stability of SATACs and the maintenance of the SATACs across generations. DECLARATION 7 further evidences the stability by data showing that the SATACs generated in *Brassica napus*, upon transmission in regenerated

plant, exhibit a segregation pattern at a predicted Mendelian frequency. The results of these analyses demonstrate that the methods described in the above-referenced application can be used to generate, identify and maintain plant SATACs in plant cells.

II. The Rejection of Claims 50-52, 73-115 and 117-127 Under 35 U.S.C. §112, First Paragraph – Written Description

Claims 50-52, 73-115 and 117-127 are rejected under 35 U.S.C. §112, first paragraph for alleged lack of written description, because it is alleged that the specification does not describe the subject matter in such a way as to convey to one skilled in the relevant art that the inventor(s) had possession of the claimed subject matter at the time the application was filed. The Examiner urges that the specification only provides guidance for a satellite artificial chromosome in mammalian cells, specifically mouse cells, and does not provide guidance for any plant artificial chromosomes, sequences, or methods of making same, or any plant cells comprising any artificial chromosomes. The Examiner cites case law to allege that the written description of the claimed subject matter has not been satisfied. This rejection respectfully is traversed.

As noted above, in the Office Action at page 2-7 under "Response to Arguments" and again at pages 13-21 of the Office Action, the Examiner also addresses Applicant's arguments made in the previous Response mailed April 30, 2007. In addressing Applicant's arguments, the Examiner has not separated rejections for enablement and written description under 112, first paragraph. Since the standards and the law differ between such rejections, the Examiner's "Response to Arguments" as Applicant finds they relate to alleged lack of written description are rebutted in turn below. The Examiner's other "Response to Arguments" were rebutted above under the 112, first paragraph lack of enablement rejection.

Relevant Law

The case law has been discussed in previous responses and is incorporated by reference herein.

The claims

Independent claim 92 is drawn to a method of producing a transgenic plant by introducing a SATAC into a plant cell. Dependent claims recite particulars of the SATACs or methods.

Analysis

The remarks/arguments and relevant law provided in previous responses, including the last response submitted April 30, 2007, directed to lack of written description of the

claimed subject matter is incorporated by reference herein. As discussed in previous responses, the application provides a detailed description of preparation of SATACs, including drawings, detailed description and working examples. The description of SATACs and methods of generating SATACs as described in the specification is generic, and is not limited to a single species. Exemplary SATACs and cell lines are deposited. Furthermore, SATACs are generically claimed in the originally filed application and are generically claimed in issued patents, evidencing the Office's determination that applicant had possession of a broader genus. This is evidenced by the DECLARATIONS, which evidence the broad applicability of the methods.

Although the working examples are exemplified in animal cells, the application explains that methods of generating satellite artificial chromosomes are applicable to any plant and animal cell type and any plant and animal species of satellite artificial chromosomes (see for example, at page 9, lines 14-18; at page 12, lines 8-9; and at page 16, lines 27-29). For example, at page 9, lines 14-18, the specification states:

> Thus, methods for producing MACs of both types (i.e. SATACs and minichromosomes) are provided. These **methods are applicable to the production of artificial chromosomes** containing centromeres derived **from any higher eukaryotic cell, including mammals, birds, fowl, fish, insects and plants.**

In particular, the specification describes plants, including tobacco, monocots and dicots as exemplary hosts to which heterologous DNA can be introduced. As described in the specification, the exemplified methods can be used in any such host cells to "produce species-specific artificial chromosomes," (see e.g., at page 51, line 27 to page 52, line 10.) The specification describes in great detail methods of introducing the DNA, including artificial chromosomes into plant cells using a variety of techniques. For example, the specification describes that if the artificial chromosome is contained within a cell, it can be introduced by cell fusion or microcell fusion. Other techniques include, but are not limited to, direct DNA transfer, electroporation, lipid-mediated transfer, microprojectile bombardment, microinjection or PEG-induced DNA uptake, see, for example, at page 48, line 11 to page 56, line 21, which include description of introducing artificial chromosomes into plants or heterologous DNA into plants to generate SATACs using the methods described in the application. Further, the instant application demonstrates possession of plant satellite artificial chromosomes as of the earliest filing date of the application. The specification describes that plant satellite artificial chromosomes have the same structural

elements as described for mammalian artificial chromosomes, except that they have a plant centromere (see for example, at page 16, line 27-29).

In the instant Office Action, the Examiner cites University of California v. Eli Lilly. 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) for the premise that naming a material is not adequate written description. A similar rejection was raised in the Office Action mailed October 22, 2003, and addressed in the response thereto dated April 22, 2004 (see page 17 of that response). Nevertheless, the rejection is addressed again herein below.

It respectfully is submitted that unlike Eli Lilly, however, where the cDNA was not described by structural features, id. at 1567, as discussed in detail in previous responses, the instant application describes in great detail the structural and functional features of SATACs, including plant SATACs. The specification describes in extensive detail the preparation, characterization and isolation of satellite artificial chromosomes and types thereof such as megachromosomes, and provides numerous examples of particular embodiments thereof and cells containing particular embodiments thereof.

Furthermore, the court stated in Eli Lilly, that a description of a genus may be achieved by providing structural features common to the members of the genus. Id. At 1569. This test for the written description requirement is reiterated in the MPEP §2163, which states that an adequate written description for a claimed genus need only provide "relevant, identifying characteristics" of a representative number of species. The instant application clearly describes the relevant identifying characteristics of SATACs, and their preparation. As discussed in detail in previous responses, SATACs are described by their structural elements, including as containing more heterochromatin than euchromatin, typically predominantly heterochromatin, and also other features including centromeres, telomeres, an origin or replication. The specification details their preparation and schematically describes the intermediates that occur in the generation of SATACs. The DECLARATIONS of record, including DECLARATION 5 of Fabijanski, show that, as described in the specification, these intermediates, as well as the resulting satellite artificial chromosomes occur in plants. Plant SATACs are further described as a species of a SATAC containing a plant centromere (see, for example, at page 16, lines 27-29). As discussed above, the application provides a highly reproducible elegant and simple method for generating SATACs in plants and animals; the DECLARATIONS demonstrate that plant SATACs and animal SATACs have been reproducibly made following the methods of the specification.

Thus, Applicant has complied with the expectations set forth in the written description requirement by describing the relevant, identifying structural features of SATACs that are common to the genus. Furthermore, as demonstrated in the DECLARATIONS, all one of skill in the art has to do is introduce a DNA fragment into a cell, grow the cell under selective conditions, and "poof" SATACs and/or precursors or intermediates thereof are produced by the cell. One of skill in the art has merely to select cells that have a SATAC or other desired intermediate or precursor or chromosomal structure. Therefore, Applicant has sufficiently described SATACs such that they can be used in the claimed methods for introducing a SATAC into a cell.

The Office Action also cites Amgen Inc. v. Chugai Pharmaceuticals Co., 927 F.2d 1200 (Fed. Cir. 1991) to state the written description is not satisfied in the absence of chemical and physical properties of the product. Amgen is inapt with respect to the instant application. Amgen does not address the facts herein in which species of the claimed genus were isolated and exemplary species deposited. In fact, in Amgen, in one of the patents at issue U.S. Patent No. 4,703,008, claim 2, which was held to be valid recites:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding erythropoietin.

Thus, the name of the protein, erythropoietin, presumptively provides adequate written description of the molecule. Sequence and/or structural information was not described in the claims.

Furthermore, in the instant case, the description of satellite artificial chromosomes provided in the instant application identifies the actual physical embodiments of a plant satellite artificial chromosome generated using methods described in the application. The DECLARATION 5 of Fabijanski describes the results of analyses of cells obtained by transfection of two different species of plants, *Nicotiana* and *Brassica*, with heterologous DNA. Through those analyses, which included fluorescence in situ hybridization (FISH) for visualization of pericentric heterochromatin and the heterologous DNA, identification a plant satellite artificial chromosome was based on the description of a plant satellite artificial chromosome in the application. As set forth in Fabijanski DECLARATION 5, a comparison of DAPI-stained chromosomes from cells introduced with the heterologous DNA and the results of FISH analyses of the same chromosomes using a FITC-labeled probe specific for a portion of the heterologous DNA (i.e. selectable marker) and a rhodamine red-labeled probe specific for pericentric heterochromatin (18s rDNA) revealed the entire plant artificial

chromosome hybrid. In addition, as discussed above, no sequence information is employed in preparing or identifying satellite artificial chromosomes.

Finally, the pertinence of the Examiner's citation of MPEP §2163 is not clear. The instant specification as discussed herein provides detailed description of the structure of a satellite artificial chromosomes, and teaches how to prepare, identify and isolate them. Furthermore, in an abundance of caution, cell lines carrying exemplary satellite artificial chromosomes were deposited, assuring that one of skill in the art has access to exemplary satellite artificial chromosomes and further evidencing possession thereof. Hence reliance on this paragraph in the MPEP is misplaced.

Conclusion

The written description requirement can be satisfied without providing representative species of every type of satellite artificial chromosomes, if the descriptions provided therein are descriptive of all satellite artificial chromosomes. As noted above, the application indicates the characteristics of satellite artificial chromosomes described therein are applicable to all eukaryotic satellite artificial chromosomes. The specification explicitly states that plant satellite artificial chromosomes can be made by the methods therein. Thus, the detailed descriptions of structural and functional characteristics of satellite artificial chromosomes are directly applicable to plant satellite artificial chromosomes. Moreover, the satellite artificial chromosomes and cells containing satellite artificial chromosomes provided in the specification are exemplary of plant satellite artificial chromosomes, since, as described, the identifying characteristics and methods for their production are common to all satellite artificial chromosomes. Such disclosures evidence Applicant's possession of plant satellite artificial chromosomes and cells containing such chromosomes. Therefore, it is respectfully submitted that Applicant had possession of the claimed subject matter as the time the instant application was filed.

Rebuttal to Examiner's Comments

A. The Application generically describes SATACs, and methods of making SATACs, in any eukaryotic species, including plants.

The Examiner states that only the demonstration and description of mammalian SATACs and mammalian cells is present in the specification, and that Applicant has not satisified the Written Description requirement with respect to plants by either 1) describing an actual reduction to practice; 2) a clear depiction in a drawing; or 3) a description of

identifying characteristics. Thus, the Examiner urges that Applicants have not demonstrated possession of the claimed subject matter.

Applicant disagrees with the Examiner's statement. The application describes a universal process for the generation of SATACs. As described in the application, introduction of nucleic acid into a cell, which gets incorporated into a chromosome initiates amplification events, leading to the generation of a *de novo* centromere, resulting in intermediate chromosome structures such as a dicentric chromosome and sausage chromosome, and ultimately a SATAC. Introduction of the DNA fragment under conditions in which the amplification event will be observed, such as growth under selective conditions, is all that is required to initiate the process. Introduced nucleic acid will, by chance incorporate into the heterochromatic pericentric region of a chromosome; or the probability can be increased by targeting it, such as by inclusion of rDNA sequence in the fragment. DECLARATION 6 of Hadlaczky further evidences the universality of the process of generating SATACs. As described in DECLARATION 6, the processes underlying the generation of SATACs are fundamental to all eukaryotic species, and are as described in the application. Other DECLARATIONS, including DECLARATION 5 and 7 (provided herewith) evidence that by using methods as set forth in the specification, plant SATACs are generated.

The application provides working examples of the generation of SATAC using mouse cells, but describes that the phenomenon is generalizable and applicable to other eukaryotic cells (see e.g., at page 30, lines 9-12; and at page 36, lines 3-4). The specification describes that the method can be to generate species-specific artificial chromosomes (see e.g., at page 51, line 27 to page 52, line 10 under "Hosts") depending on the cell used to introduce the heterologous DNA. Additionally, the application provides working examples of these methods. Although the working examples are exemplified in animal cells, the application explains that methods of generating satellite artificial chromosomes are applicable to any plant and animal cell type and any plant and animal species of satellite artificial chromosomes (see for example, at page 9, lines 15-19; page 30, lines 9-12). For example, at page 9, lines 15-24, the specification states:

> Thus, methods for producing MACs of both types (i.e. SATACs and minichromosomes) are provided. These methods are applicable to the production of artificial chromosomes containing centromeres derived from any higher eukaryotic cell, including mammals, birds, fowl, fish, insects and plants.

> The resulting chromosomes can be purified by methods provided herein to provide vectors for introduction of heterologous DNA into selected cells for production of the gene product(s) encoded by the heterologous DNA, for production of transgenic (non-human) animals, birds, fowl, fish and plants or for gene therapy.

While the exact phrase "plant SATAC" does not appear in the specification, numerous references to plants and to the use of the enabling methods in plants to generate species-specific artificial chromosomes renders it absolutely clear that the method of generating SATACs, and the resulting SATACs, is universal and applicable in all eukaryotic species, including plants. The instant application also demonstrates possession of plant satellite artificial chromosomes as of the earliest filing date of the application. The specification describes that plant satellite artificial chromosomes are satellite artificial chromosomes that include plant centromeres (see for example, at page 16, lines 22-36).

Applicant has provided detailed identifying characteristics of SATACs that are applicable to plant SATACs. The application makes clear that the common attributes possessed by the members of the genus of satellite artificial chromosomes are relatively invariant. Furthermore, all arise by the amplification events as described in the application. The application describes that, except for the heterologous nucleic acid such as a selectable marker or other foreign DNA, the SATACs contains only non-protein-encoding heterochromatin (see page 7, lines 17-22). The application describes that this megachromosome (i.e. SATAC) is stable and can replicate and segregate alongside an endogenous chromosome (see, e.g., page 16, lines 22-35; page 34, line 23). The application describes how generate a satellite artificial chromosomes, how to identify a satellite artificial chromosome, for example, by C-banding and/or fluorescence in situ hybridization (FISH) using labeled nucleic acid probes (e.g., satellite DNA probes) to visualize heterochromatin and highly repetitive DNA. The instant application provides elaborate descriptions of an exemplary satellite artificial chromosome (i.e. a mouse megachromosome) that was generated in a mouse cell line, which included C-banding studies and FISH analyses showing that these satellite artificial chromosomes contain repeating units of satellite DNA. The same methods can be applied to any satellite artificial chromosome produced in any cell type. Furthermore, the DECLARATIONS of record, discussed above, provide confirmatory evidence to rebut any statement by the Office that plant satellite artificial chromosomes would have a different structure or would not be generated as described in the application.

The written description requirement can be satisfied without express or explicit disclosure of the claimed subject matter. See e.g., In re Herschler, 591 F. 2d 693, 700, 200 USPQ 711, 717 (CCPA 1979); Purdue Pharma L.P. v Faulding, Inc. 230 F.3d 1320, 1323, 56 USPQ 2d 1481, 1483 (Fed. Cir. 2000). As noted above and described in detail in previous responses, the application indicates the characteristics of satellite artificial chromosomes described therein are applicable to all eukaryotic satellite artificial chromosomes. The specification explicitly states that plant satellite artificial chromosomes can be made by the methods therein. Thus, the detailed descriptions of structural and functional characteristics of satellite artificial chromosomes are directly applicable to plant satellite artificial chromosomes and other eukaryotic species.

Finally, the specification demonstrates production of satellite artificial chromosomes per se. A satellite artificial chromosomes is a satellite artificial chromosomes whether or not it is generated in a plant or animal cell. The methods and processes and resulting products are not kingdom specific, but are universal.

B. The DECLARATIONS of record demonstrate generation of SATACs in plants as described in the application

The Examiner urges that the DECLARATIONS of record are not persuasive to evidence generation of SATACs in plants. The main arguments provided by the Examiner in making this assertion appear to be that cytological techniques that would be required for plant cells are different from mammalian cells, and are not adequately described in the specification. The Examiner further urges that evidence of a plant centromere is required to evidence generation of a plant SATAC, since, in order to be stably maintained, a plant centromere is required. The Examiner notes that such sequences and structures and functions were not known in plants as of the earliest filing date.

First, it is respectfully submitted that Applicant is not claiming cytological methods, nor are cytological methods per se required to generate or isolate a SATAC. Cytological techniques, however, allow visualization of SATACs. The application describes cytological techniques for visualization of SATACs including in situ hybridization and other techniques (see e.g., Example 4-6). As discussed above and demonstrated in DECLARATION 7, such cytological techniques in plants were well known at the time of filing the application (see *e.g.*, Leitch *et al.* (1991) *Genome*, 34:329-333; Fukui *et al.* (1994) *Theor. Appl. Genet.*, 87:893-899; Jiang *et al.* (1995) *Proc. Natl. Acad. Sci.* USA, 92: 4487-4491; Murata and Motoyoshi (1995) *Chromosoma*, 104:39-43; Matsuyama *et al.* (1996) *Genome*, 39:941-945;

Zhong *et al.* (1996) *Chr. Res.*, 4:24-28; and Schubert I and Wobus U (1985) *Chromosoma*, 92: 143-148).). As set forth in MPEP 2163.II.A.2, a review of written description is conducted from the standpoint of one of skill in the art at the time the application was filed, and should include a determination of the field of the invention and the level of skill in the art. Information which is well known in the art need not be described in detail in the specification. Thus, this issue is not dispositive to the presently claimed subject matter.

Second, as discussed above and in the previous response, it is respectfully submitted that there is no need to provide sequence information or conservation of sequence. Satellite artificial chromosomes are generated by amplification events that occur upon integration of a DNA fragment in the heterochromatic pericentric region of the chromosome. It is the functional structural features that are key, not the particular sequences. Thus, sequence information is not needed to prepare satellite artificial chromosomes nor to identify them. SATACs can be identified based on in situ analysis evidencing the presence of a separate chromosome structure containing predominantly heterochromatin and heterologous DNA, and a centromeric constriction. This is evidenced in the DECLARATIONS.

Plant chromosomes do have centromeres, and SATACs, including plant SATACs, contain centromeres as described in the application. The inclusion of a plant centromere in the SATAC occurs by virtue of the amplification events, that can include duplication of the centromere, leading to production of a formerly dicentric chromosome. The amplification events occur upon practice of the methods. As set forth in both DECLARATIONS 5 and 7 (provided herewith), no knowledge of centromere sequence is required. By virtue of the method, the resulting SATACs contain a functional centromere as evidenced by the stability of SATACs and the maintenance of the SATACs across generations as discussed above and demonstrated in DECLARATIONS 5 and 7.

The description of SATACs provided in the instant application describes SATACs, including plant SATACs. The DECLARATIONS of record, including DECLARATION 5 and DECLARATION 7, depict SATACs obtained using methods as described in the application. Hence, plant SATACs are sufficiently described in the instant application to demonstrate Applicant's possession of these artificial chromosomes.

III. Rejection of Claims 50-52, 73, 80, 88-92, 94-96, 98-100, 107, 114, 117-118 and 120-122 Under U.S.C. §102(b)

Claims 50-52, 73, 80, 88-92, 94-96, 98-100, 107, 114, 117-118 and 120-122 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Richards *et al.* (U.S.

Patent No. 5,270,201, issued 14 December 1993), which is alleged to teach an artificial plant chromosome and methods of transforming it into plant cells. In particular, the Examiner states that Applicant's arguments are unpersuasive, since the claims are not drawn to artificial chromosomes that are predominantly heterochromatic. This rejection respectfully is traversed.

Relevant law

The case law has been discussed in previous responses and is incorporated by reference herein.

The rejected claims

Independent claim 92 is directed to a method for producing a transgenic by introducing a SATAC into a plant cell, wherein the SATAC contains **more heterochromatin than euchromatin**, and growing the plant cell under conditions to produce a transgenic plant. All other rejected claims are dependent on claim 92 and recite particulars of the method. Hence, the claims recite that the SATAC that is introduced into a plant cells contains more heterochromatin than euchromatin.

As set forth in previous responses and as described in detail in the specification, a SATAC is a chromosomal structure first identified and characterized by Applicants. As described in detail in the application, a SATAC is produced by an amplification event upon introduction of heterologous DNA into cells, growing the cell and then selecting those cells that have a SATAC based on its identifying characteristics, such as being predominantly heterochromatic. The specification defines a SATAC as:

> As used herein, a SATAC refers to a chromosome that is substantially all heterochromatin, except for portions of heterologous DNA. Typically, SATACs are satellite DNA based artificial chromosomes, but the term encompasses any chromosome made by the methods herein that contains more heterochromatin than euchromatin.

Claims are to be read in light of the specification, and therefore, the recitation of SATAC in the claim renders it clear that the artificial chromosome structure contains more heterochromatin than euchromatin. Nevertheless, to advance prosecution, claim 92, and claims dependent thereon, are amended to specify that the SATAC that is introduced into the plant cell contains more heterochromatin than euchromatin.

Differences between the disclosure of Richards *et al.* and the rejected claims

Richards *et al.* describes isolation of a telomeric clone from A. thaliana and methods for obtaining autonomous replicating sequence (ARS) and centromeric (CEN) sequences

from A. thaliana. Richards et al. also discloses construction of plant artificial chromosomes using a vector containing ARS and CEN sequences. Example 19, which is prophetic, purports to provide a method for assembling the telomeres, ARS and centromere into an artificial chromosome.

Richards *et al.* does not disclose a method for producing a transgenic plant by introducing a SATAC into a plant cell. Richards *et al.* does disclose making SATAC. Richards *et al.* does not even disclose a method of making a SATAC nor any method involving introducing a DNA fragment containing a selectable marker into a cell, growing the cells and selecting a cell that contains a SATAC, which is a chromosome that contains more heterochromatin than euchromatin. There is no disclosure in Richards et al. of a method in which heterochromatin is amplified to produce a SATAC containing more heterochromatin than euchromatin.

Thus, Richards et al. does not disclose a method of introducing a SATAC into a plant cell and growing the cell to generate a transgenic plant. Therefore, Richards *et al.* fails to disclose all elements as claimed Thus, Richards *et al.* does not anticipate any of claims 50-52, 73, 80, 88-92, 94-96, 98-100, 107, 114, 117-118 and 120-122, nor any pending claim. Accordingly, Applicant requests reconsideration of this rejection.

IV. Rejection for Obviousness-Type Double Patenting

RELEVANT LAW

Obviousness-type double patenting occurs when that the difference between a first-patented invention and its variant involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. See, *e.g.*, *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 23 USPQ2d 1839, 1845 (Fed. Cir. 1992). Analysis of obviousness-type double patenting involves a comparison of the subject invention "with what invention is *claimed* in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim *defines* and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." *Id.* (emphasis in original); *see, also, Ortho Pharm. Corp. v. Smith*, 22 USPQ2d 1119, 1125 (Fed. Cir. 1992) ("It is the claims, not the specification that defines an invention [citation] . . . [a]nd it is the claims that are compared when assessing double patenting."). Thus, an obviousness-type double patenting rejection is based on the claims and not on the disclosure of a patent.

The comparison between claims in an obviousness-type double patenting inquiry requires the use of a fundamental rule of claim construction, that the invention is defined by the claim taken as a whole -- every claim limitation (or each step) being material to the description of the invention. *Ortho Pharm. Corp.*, 22 USPQ2d at 1125. Thus, it is inappropriate to base a double patenting rejection on the disclosure of a patent, even when such disclosure is found in the claims.

Obviousness-type double-patenting has not been found when the claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue. See, *e.g., Id.* Obviousness-type double-patenting only is applicable to a later issuing application and is only based upon the claims in the two cases. Furthermore, if the order of issuance results from delays in the Patent Office, not from actions of the applicant, then a two-way distinctness test must be applied. See, *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991) in which the CAFC held that in certain circumstances, a third inquiry to support an obviousness-type double rejection will only be sustained if the application claims are not patentably distinct from the prior patent claims and the prior patent claims are also not patentably distinct from the applications claims.

A. Rejection over copending U.S. Application Serial No. 10/287,313

Claims 92, 95, 99 and 114-115 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 12-13, 19-20, 26 and 52-54 and 66 of copending U.S. Application Serial No. 10/287,313. First, it is noted that rejection of the claims over Claim 20 of the copending application seems to be in error, since this claim is cancelled therein. As to the rejection over claims 52 and 66 of the copending Application, Applicant, while not conceding obviousness-type double patenting exists between these claims of the copending application and the rejected claims, it is likely that the claims in the copending application will be cancelled. Hence, for these reasons, it is premature to file a terminal disclaimer.

In addition, this rejection respectfully is traversed as to the remaining claims.

Claims

Instant Application

Claim 92, is the only independent claim in the above rejection in the instant application.

. Claim 92 recites:

> A method for producing a transgenic plant, comprising introducing a satellite artificial chromosome (SATAC) into a plant cell, wherein the SATAC contains more heterochromatin than euchromatin; and
>
> growing the plant cell under conditions to produce a transgenic plant.

Dependent claims 95, 99 and 114-115 recite particulars of the method.

Copending U.S. Application Serial No. 10/287,313

Claims 12, 13, 19, 26 and 53 are each independent claims. Claim 54 is dependent on claim 53, and recites particulars of the method of transgenic plant.

Claim 12 recites:

> A plant SATAC produced by a method comprising:
>
> introducing a DNA fragment into a plant cell, wherein the DNA fragment comprises a selectable marker;
>
> growing the cell under selective conditions to produce cells that have incorporated the DNA fragment into their genomic DNA, whereby amplification of heterochromatin occurs;
>
> selecting a plant cell that comprises a satellite artificial chromosome (SATAC); and isolating a SATAC from a selected cell.

Claim 13 recites:

> An isolated substantially pure plant satellite artificial chromosome (SATAC).

Claim 19 recites:

> A plant cell containing an artificial chromosome, wherein the artificial chromosome is produced by a method comprising:
>
> introducing a DNA fragment into a plant cell, wherein the DNA fragment comprises a selectable marker;
>
> growing the cell under selective conditions to produce cells that have incorporated the DNA fragment into their genomic DNA; and
>
> selecting a plant cell that comprises a <u>plant</u> satellite artificial chromosome (SATAC).

Claim 26 recites:

> A plant cell containing an artificial chromosome, wherein the artificial chromosome is produced by a method comprising:
>
> introducing a DNA fragment into a plant cell, wherein the DNA fragment comprises a selectable marker;
>
> growing the cell under selective conditions to produce cells that have incorporated the DNA fragment into their genomic DNA; and
>
> selecting a plant cell that comprises a <u>plant</u> satellite artificial chromosome (SATAC), wherein the SATAC is a megachromosome; and

the method further comprises, exposing the cells to conditions, whereby cells that contain truncated megachromosomes are produced.

Claim 53 recites:

A transgenic plant produced by the method of claim 52.

Analysis

Obviousness-type double patenting does not exist as between any instant claims and any of the claims 12, 13, 19, 26, 53 and 54 recited in the rejection. The instant claims are directed to a generic **method** of producing a transgenic plant by introducing a SATAC into a plant cell, and growing the plant cell under conditions to produce a transgenic plant. None of claims 12, 13, 19, 26, 53 and 54 are directed to a method, and thus are directed to subject matter distinct from the claims of the instant application. None of the claims 12, 13, 19, 26, 53 and 54 of the copending application embrace the instance claims. Furthermore, the claims are so distinct, there is no argument on which, based on rules of claim interpretation, they suggest the instant claims. Therefore, as between the claims pending in this application and the recited claims 12, 13, 19, 26, 53 and 54 from U.S. Application Serial No. 10/287,313, obviousness-type double patenting does not exist.

B. Rejection over copending U.S. Application Serial No. 11/284,877

Claims 97-92, 94-99, 114-115 and 117-121 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 41, 49, 52-53, 55, 63-65, 69-70, 73 and 76 of copending U.S. Application Serial No. 11/284,877. First, it is noted that rejection of the claims over Claim 53, 65, 69-70, 73 and 76 of the copending application seems to be in error, since these claims have been cancelled therein. As to the rejection over claim 63 of the copending Application, Applicant, while not conceding obviousness-type double patenting exists between the claim of the copending application and the rejected claims, it is likely that the claims in the copending application will be cancelled. Hence, for these reasons, it is premature to file a terminal disclaimer.

In addition, this rejection respectfully is traversed as to the remaining claims

Claims

Instant Application

Claim 92, is the only independent claim in the above rejection in the instant application and is recited above.

U.S. Application Serial No. 11/284,877

Claims 41, 52, 55 and 64 are each independent claims. Claim 49 is dependent on claim 41, and recites particulars of the method.

Claim 41 recites:

> A method for producing a plant artificial chromosome, comprising:
> introducing a DNA fragment into a plant cell, wherein the DNA fragment comprises a selectable marker;
> growing the cell under selective conditions to produce cells that have incorporated the DNA fragment into their genomic DNA; and
> selecting a plant cell that comprises a satellite artificial chromosome (SATAC).

Claim 52 recites:

> A SATAC produced by the method of claim 41.

Claim 55 recites:

> A plant cell containing the SATAC of claim 52.

Claim 64 recites:

> A transgenic plant produced by the method of claim 63.

Analysis

Obviousness-type double patenting does not exist as between any instant claims and any of the claims 41, 49, 52, 55 and 64 recited in the rejection. The instant claims are directed to a generic **method** of producing a transgenic plant by introducing a SATAC into a plant cell, and growing the plant cell under conditions to produce a transgenic plant. None of claims 52, 55 and 64 are directed to a method, and thus are directed to subject mater distinct from the claims of the instant application. Further, claim 41 is directed to a method of producing a plant artificial chromosome, which also is distinct from a method of producing a transgenic plant by introducing a SATAC into a plant cell. None of the claims 12, 13, 19, 26, 53 and 54 of the copending application embrace the instance claims. Furthermore, the claims are so distinct, there is no argument on which, based on rules of claim interpretation, they suggest the instant claims. Therefore, as between the claims pending in this application and the recited claims 12, 13, 19, 26, 53 and 54from U.S. Application Serial No. 11/284,877, obviousness-type double patenting does not exist.

In view of the above amendments and remarks, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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